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Evaluation of the Effect of Methylphenidate by Computed Tomography, Electroencephalography, Neuropsychological Tests, and Clinical Symptoms in Children with Attention-Deficit/Hyperactivity Disorder: A Prospective Cohort Study

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ABSTRACT

Background: Stimulant drugs are the most commonly used treatments for attention-deficit/hyperactivity disorder (ADHD), although the mechanism of action of these drugs is still not entirely understood.

Objective: The aim of this study was to investigate the effects of the psychostimulant drug methylphenidate (MPH) on regional cerebral blood flow (rCBF), electrical activity of the brain, and clinical symptoms in children with ADHD using single-photon emission computed tomography (SPECT), electroencephalography (EEG), and neuropsychological tests.

Methods: In this prospective cohort study, pediatric outpatients received MPH for 3 months at a mean dose of 1 mg/kg • d (range, 0.5–1.5 mg/kg • d). They were then administered the Wechsler Intelligence Scale for Children-Revised, the Bender Visual-Motor Gestalt Test (BGT), EEG, and SPECT of the brain. The parents and/or teacher of each child were asked to complete the Conners' Parent Rating Scale (CPRS), the Conners' Teacher Rating Scale (CTRS), and the Turgay *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition*-based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-*DSM-IV*-S). All of the evaluations were performed at baseline and after 3 months of MPH treatment. Each child underwent a Stroop test as an activation method 15 minutes before the SPECT procedure.

Results: Sixty patients were assessed for inclusion. Twenty-one children (18 boys [85.7%], 3 girls [14.3%]; mean [SD] age, 9.7 [1.7] years; range, 8–13 years) with a diagnosis of ADHD were included in and completed the study. Mean (SD) BGT scores before MPH treatment compared with after MPH treatment were significantly decreased (9.8 [4.2] vs 6.3 [3.4]; Z = –3.27; P = 0.001). After

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treatment with MPH, the visual SPECT results suggested that low rCBF was normalized in the right frontotemporal areas in 10 children with ADHD. After treatment, 12 patients (57.1%) had no change in EEG activity, 5 (23.8%) had improvement, and 4 (19.0%) had worsening activity. Patients who had improvement or no worsening on EEG after MPH treatment were associated with significant improvement after MPH treatment compared with before treatment in mean (SD) CTRS scores (25.9 [14.3] vs 35.0 [14.4]; $P = 0.003$), teachers' T-*DSM-IV*-S total score (25.1 [14.2] vs 38.4 [18.7]; $P = 0.005$), and CPRS scores (mothers scores: 29.7 [16.6] vs 42.6 [17.2], $P = 0.002$; fathers' scores: 29.4 [16.8] vs 41.9 [23.7], $P = 0.004$). No significant difference was found in these scores in the patients whose EEG findings showed deterioration after MPH treatment. The quantitative values for SPECT observed before treatment compared with those observed after 3 months of MPH treatment were not found to be significantly different in any areas of the brain.

Conclusions: MPH use over 3 months was associated with improvement from baseline in visual-motor function and behavioral disorders in these children and adolescents with ADHD. However, no significant difference in rCBF or electrical activity in the brain was observed in this small study. (*Curr Ther Res Clin Exp.* 2007;68:432–449) Copyright © 2007 Excerpta Medica, Inc.

Key words: attention-deficit/hyperactivity disorder, single-photon emission computed tomography, electroencephalography, methylphenidate.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD), which is a neuropsychiatric disorder that begins before 7 years of age, affects 3% to 5% of school-aged children and plays an important role in disorders of social, emotional, and cognitive development.[1] ADHD demonstrates itself through the core symptoms of attention deficiency, hyperactivity, and impulsivity.[2] For >50 years, psychostimulant drugs have been used to treat these core symptoms. Clinical and experimental studies with placebo controls have demonstrated that ~80% of patients with ADHD made significant clinical recovery with psychostimulant therapy.[3,4] The mechanisms of action of these stimulants in the treatment of ADHD, including their neurophysiologic effects, as well as associated adverse events (AEs), remain topics for research.[5,6]

Methylphenidate (MPH) is an effective short-term psychostimulant with a 2- to 3-hour $t_{1/2}$, the effects of which last ~1 to 4 hours after administration. Although the mechanism of action of MPH is not well-known, it is believed that among the neurotransmitters in the frontostriatal areas of the brain, it especially affects the reuptake and release of dopamine.[7] MPH is thought to increase the degree of attention control in children with ADHD and to decrease the behaviors of opposing and excessive activity by maintaining the increased dopamine level.[4,7] In a study[8] of the effect of MPH treatment on the academic success of children with ADHD, their performance in mathematics improved

significantly due to improvement in executive functioning and working memory. In studies[9,10] of the effects of MPH on the success of children with ADHD on neuropsychological tests, improvement was observed in various areas of executive functioning (eg, spatial working memory, set shifting, cognitive elasticity, and planning). In children with ADHD who had been receiving long-term stimulant treatment, significant declines were found in mistake scores on neuropsychological tests caused by impulsivity and lack of attention.[11]

Brain imaging techniques have been used in ADHD research since the late 1980s.[12,13] Converging evidence from structural and functional imaging studies implicates abnormalities in the frontostriatal network as the likely cause of ADHD.[14] A functional imaging study[15] reported hypoperfusion in the frontal lobe and striatum and hyperperfusion in the somatosensory cortex and occipital cortex in the baseline condition. Abnormal activation patterns during mental tasks have also been found.[16] Abnormal asymmetry, especially dysfunction of the right prefrontal region within the frontostriatal network, has been implicated in hyperactivity and inattentiveness.[17,18] Imaging studies[19,20] investigating differences in regional cerebral blood flow (rCBF) levels before and after oral MPH treatment in children with ADHD have been reported only rarely. In a study by Kim et al,[19] the left and right prefrontal areas, and caudate and thalamic areas showed significant increases in rCBF after MPH treatment. In the study by Lee et al,[20] MPH treatment also resulted in rCBF increase in the superior prefrontal area and reduction in ventral higher visual areas bilaterally.

In an attempt to better understand the actions of stimulant medications in children with ADHD, the changes in electroencephalography (EEG) due to the administration of stimulants have been investigated. Chabot et al[21] found that 56.9% of 130 children with ADHD showed normalization of EEG activity after the administration of a stimulant, 33.8% showed no change, and 9.3% showed an increase in EEG abnormalities. Behavioral improvement after stimulant treatment was seen in 81.5% of the children with ADHD and 44.7% of the children with attention-deficit disorder, with the degree of correspondence between behavioral and quantitative EEG changes at 78.5%. Pretreatment clinical and quantitative EEG features could predict treatment response with a sensitivity of 83.1% and a specificity of 88.2%. Swartwood et al[22] and Lubar et al[23] investigated the effects of MPH in 23 boys with ADHD, but did not identify any global changes in EEG activity associated with treatment. In another study in children with ADHD who had a positive reaction to stimulant treatment, an increase in beta activity in the frontal areas, a decrease in theta and alpha waves, and a significant correlation between changes in beta activities and improvement on neuropsychological tests were reported. Another study examined EEG changes associated with a double-blind, placebo-controlled administration of MPH among 10 children, ages 8 to 13, with a primary diagnosis of ADHD. As a result of this study, an increase in beta activity in the frontal areas, a decrease in theta and alpha waves, a significant correlation between changes in beta activities, and improvement on neuropsychological tests in children who had a positive

reaction to stimulant treatment, were reported ($P < 0.05$).[24] However, a limitation of that study was that the population comprised only 10 patients with ADHD.

The aim of the present study was to examine MPH-induced changes in rCBF, electrical activity of the brain, and clinical symptoms in children with ADHD to determine the site of action of MPH using single-photon emission computed tomography (SPECT), EEG, and neuropsychological tests.

PATIENTS AND METHODS

Patients

In this prospective cohort study, the study participants were selected from among children who applied to the Child and Adolescent Psychiatry Department outpatient clinic at the Kocaeli University School of Medicine, Kocaeli, Turkey. Prior to the study, its nature and purpose were fully explained to the patients and their parents, and written informed consent was obtained from each child's parent and written assent from each child for all procedures. The Ethics Committee of Kocaeli University approved the study protocol, and the study followed the principles of the Declaration of Helsinki[25] and the Guidline of Good Clinical Practice.[26]

At least 1 certified child psychiatrist and 1 child psychologist evaluated each patient. All patients included in this study received a clinical diagnosis of ADHD based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*).[2] Children with a diagnosis of ADHD of combined subtypes who were right-handed (in order to prevent dominant hemisphere difference) were eligible for the study. None of the patients had previously been diagnosed with ADHD, nor had they been treated with psychopharmacologic drugs. Patients were eligible for the study if they had an unremarkable medical history except for ADHD. Patients were clinically screened and excluded for psychoses, eating disorders, substance abuse, pervasive developmental disorders, depression, anxiety, epilepsy, and mental retardation. Intellectual and learning abilities were assessed using the Turkish version of the Wechsler Intelligence Scale for Children-Revised (WISC-R).[27] Behavioral and emotional problems were assessed using the Conners' Parent Rating Scale (CPRS),[28] the Conners' Teacher Rating Scale (CTRS),[29] and the Turgay *DSM-IV*-based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-*DSM-IV*-S),[30] which have been standardized in Turkish.

Compliance was evaluated based on reporting by the parents at the monthly control meetings. The patients and parents were questioned during the monthly clinical evaluations regarding any AEs.

Neuropsychological Instruments

Wechsler Intelligence Scale for Children-Revised

The WISC-R, developed by Wechsler,[31] was adapted to Turkish with a standardization study conducted by Savasır,[27] which included 1639 children from 11 different

city centers. The WISC-R provides 3 measurements in 3 sections: (1) general intelligence score; (2) verbal intelligence score; and (3) performance intelligence score.

Stroop Test

Valid, reliable studies of the Stroop test[32] have been conducted in Turkey by Karakas.[33] The Stroop test measures the capability of an individual to maintain attention on 1 of 2 competing stimuli by suppressing the other. It measures whether patients can change their existing perception of changing desires. The Stroop test is used to evaluate the suppression of stimuli that distract attention (interference resistance) and the strength to keep the response waiting for the inappropriate stimuli. The test consists of 5 sections in which 4 cards are presented in a fixed order. In the first 2 sections, the words on the cards are to be read. In the other 3 sections, the colors of the words or forms are to be named. The duration of reading rate and the number of mistakes and corrections made are recorded for each section on the Stroop standard registration form. Therefore, 5 different completion durations and mistake and correction scores are obtained.[34]

Bender Visual-Motor Gestalt Test

The Bender Visual-Motor Gestalt Test (BGT) is a developmental test used to measure visual motor functioning. Specifically, it measures perception of the visual stimulant, visual motor coordination, and integration. Koppitz[35] evaluated and interpreted the test. Norms valid for children aged 6 to 13 years were determined by Yalin.[36] The scoring system, which was developed by Koppitz, is based on the number of mistakes made. The mistakes are classified into 4 groups—rotation, merging, shape distortion, and repetition.

T-DSM-IV-*S*

The T-*DSM-IV*-S was developed by Turgay[37] and adapted and translated into Turkish by Ercan et al.[30] The T-*DSM-IV*-S is based on the *DSM-IV* diagnostic criteria and assesses hyperactivity-impulsivity (9 items), inattention (9 items), opposition-defiance (8 items), and conduct disorder (15 items). A severity estimate is assigned for each symptom on a 4-point Likert scale (0 = not at all; 1 = just a little; 2 = quite a bit; and 3 = very much). Subscale scores on the T-*DSM-IV*-S are calculated by summing the scores on the items in each subscale. Although validity and reliability of this scale are not validated in Turkey, a very similar scale, the ADHD Rating Scale IV, has been found to have adequate criterion-related validity and good reliability in different cultures as determined by both parents and teachers.[38,39]

Conners' Parent Rating Scale

The 48-item Turkish form of the CPRS was translated and adapted by Dereboy et al.[28] The 4 indices in the test are as follows: (1) hyperactivity/impulsivity; (2) inattention; (3) opposition/defiance; and (4) conduct disorder. In rating his

or her child's behavior, the parent responds to each item on a 4-point Likert scale (0 = never; 1 = rarely; 2 = often; and 3 = always). The reliability and validity of the Turkish form of the CPRS in screening attention-deficit and disruptive behavior disorders was demonstrated by Dereboy et al.[40]

Conners' Teacher Rating Scale

The 28-item CTRS was developed by Goyette et al[41] and was translated into Turkish by Sener et al.[29] The teacher ratings are scored on a 4-point Likert scale (0 = never; 1 = rarely; 2 = often; and 3 = always). The reliability and validity of the Turkish form of the CTRS in screening attention-deficit and disruptive behavior disorders was demonstrated by Sener et al. Based on the authors' recommendations, the total score was used instead of the subscale scores.

Design and Procedure

Prior to beginning MPH treatment, various questionnaires were given to the patients, parents, and teachers. After the patients completed the psychometric testing and before they began MPH treatment, they underwent the first brain SPECT and EEG. Patients then received MPH for 3 months at a mean dosage of 1 mg/kg • d (range, 0.5–1.5 mg/kg • d). All patients underwent repeat psychometric testing, SPECT, and EEG at the end of the 3-month treatment period. On the day of the second SPECT scan, MPH was administered 90 minutes before ^{99m}technetium ethyl cysteinate dimer (^{99m}Tc-ECD) was injected and an EEG was performed. ^{99m}Tc-ECD was injected and the Stroop test was administered as the activation method 30 minutes before the SPECT assessment.

Single-Photon Emission Computed Tomography Imaging Protocol

During the procedure, patients were placed in the supine position in a quiet room. All patients received an ^{99m}Tc-ECD injection in the appropriate dose (10–15 mCi) based on their weight under stable conditions without sedation while the Stroop test was being administered. SPECT was performed using a single-head gamma camera with a low-energy, high-resolution, parallel-hole collimator (Adoc Laborataries, Milpitas, California). The energy window was set to 140 KeV with a 15% width. Sixty-four frames were acquired in step-and-shoot mode, with each frame continuing for 30 seconds. The matrix size was 128 × 128. Raw images were reconstructed using filtered black projection (Ranp Hamming filter cutoff frequency: 0.35; order: 5). All images were corrected for attenuation using the Chang method and were evaluated visually and quantitatively.[42] For the quantitative analysis of the 4-pixel–thick transaxial slices, circular regions of interest were drawn on both hemispheres symmetrically from the cerebellum and the frontal, temporal, parietal, and occipital cortices. Quantitative values were obtained by normalizing the counts in the regions of interest according to the cortex, thereby calculating the difference between the left and right hemispheres based on the values of the right hemisphere.

The quantitative values obtained before treatment were compared with those obtained after 3 months of treatment with MPH.

SPECT shows the dispersion of radionuclides in the body in 3 dimensions.[43] The fact that rCBF reflects regional neural activity, and therefore metabolism, provides the pathophysiologic basis of brain-perfusion SPECT imaging. SPECT provides information about the functioning of the brain that is complementary to the detailed structural visualization provided by radiologic methods such as computed tomography and magnetic resonance imaging.[44]

Electroencephalography Imaging Technique

Silver disc electrodes were placed on the scalp of each patient. Readings were done with 8 channels and a 10–20 location system for electrode placement on the scalp. The EEG lasted 20 minutes. Hyperventilation was applied for 3 minutes and photic stimulation was applied at 1 to 50 Hz on odd and even frequencies.

EEG is the gold standard used in the examination of patients who have or are suspected of having seizures.[45] EEG is used to measure electrical activity in the brain; waves of different frequencies and amplitudes are recorded by electrodes at standardized positions.

Statistical Analysis

Statistical analysis was performed using SPSS 10.0 for Windows (SPSS Inc., Chicago, Illinois). Apart from descriptive statistical methods (mean [SD]), the Wilcoxon signed rank test was used because the groups did not show a normal distribution in the comparison of binary groups variant in quantity. Differences in quality were compared using the χ^2 test. The results are provided within a 95% reliability range; $P \leq 0.05$ was considered statistically significant. A power calculation was not done because of the small size of the study population. Adjustments were not done for multiple comparisons.

RESULTS

Sixty patients with a diagnosis of ADHD were assessed for inclusion. Twenty-one Turkish children (85.7% [18] boys, 14.3% [3] girls; mean [SD] age, 9.7 [1.7] years; range, 8–13 years) participated in and completed the study. Thirty-nine patients were excluded from the study because they refused to take part in SPECT evaluation, which is an invasive procedure that was scheduled to take place after 3 months. Demographic and clinical characteristics are presented in **Table I**. Based on reporting by the parents at the monthly control meetings, none of the patients were noncompliant for >2 days during the follow-up period.

Total mean (SD) score on the WISC-R for all children was 97.1 (14.1) and range was from 80 to 128.

The second subcategory of the Stroop test, which measures reading rate, decreased significantly after MPH treatment ($Z = -2.242$; $P < 0.05$). There were

Table I. Baseline demographic and clinical characteristics of the study patients (N = 21).

Characteristic	Value
Age, y	
Mean (SD)	9.7 (1.7)
Range	8–13
Sex, no. (%)	
Male	18 (85.7)
Female	3 (14.3)
WISC-R (total score)	
Mean (SD)	97.1 (14.1)
Range	80–128
Comorbidity, no. (%)	
LD	5 (23.8)
ODD	2 (9.5)
NE	2 (9.5)
MPH dose, mg/kg • d	
Mean	1
Range	0.5–1.5

WISC-R = Wechsler Intelligence Scale for Children-Revised; LD = learning disorder; ODD = opposition defiance disorder; NE = nocturnal enuresis; MPH = methylphenidate.

no other significant differences observed in the other subcategories of the Stroop test.

Mean (SD) BGT scores before MPH treatment compared with after MPH treatment were significantly decreased in the 21 study participants (9.8 [4.2] vs 6.3 [3.4]; Z = –3.27; $P = 0.001$) (**Table II**).

Compared with pretreatment scores, the mean scores on the T-*DSM-IV*-S completed by the mothers and the teachers decreased significantly after MPH treatment for hyperactivity/impulsivity (12.3 [6.2] vs 7.7 [5.4], $P = 0.005$ and 11.4 [6.2] vs 8.4 [6.4], $P = 0.044$, respectively), oppositional defiant disorder (7.9 [4.3] vs 6.2 [4.9], $P = 0.025$ and 8.1 [5.3] vs 5.6 [4.8], $P = 0.050$), and total (36.5 [16.4] vs 27.0 [17.8], $P = 0.011$ and 36.9 [17.2] vs 26.9 [15.4], $P = 0.011$). On the T-*DSM-IV*-S completed by the fathers, the scores decreased significantly for oppositional defiant disorder (7.9 [5.0] vs 6.1 [4.4]; $P = 0.029$) and total (32.9 [16.2] vs 25.4 [15.9]; $P = 0.024$), while the score for hyperactivity/impulsivity did not change significantly (**Table II**).

Compared with pretreatment scores, the mean scores on the CPRS completed by the mothers and the fathers after their children were treated with MPH decreased significantly (42.2 [16.1] vs 30.6 [16.1], $P = 0.002$ and 44.0 [21.3]

Table II. Findings before and after 3 months of methylphenidate treatment on the Turgay *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*)-based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-*DSM-IV*-S), the Conners' Parent Rating Scale (CPRS), the Conners' Teacher Rating Scale (CTRS), and the Bender Visual-Motor Gestalt Test (BGT) (N = 21). Data are given as mean (SD).

Psychometric Test	Before Treatment	After Treatment	Z*	*P*
Mother				
T-*DSM-IV*-S				
Hyperactivity/impulsivity	12.3 (6.2)	7.7 (5.4)	–2.780	0.005
Inattention	13.3 (7.1)	10.3 (6.7)	–1.645	0.100
Opposition/defiance	7.9 (4.3)	6.2 (4.9)	–2.234	0.025
Conduct disorder	2.9 (4.8)	2.2 (3.7)	–1.145	0.252
Total score	36.5 (16.4)	27.0 (17.8)	–2.555	0.011
CPRS	42.2 (16.1)	30.6 (16.1)	–3.025	0.002
Father				
T-*DSM-IV*-S				
Hyperactivity/impulsivity	10.7 (6.1)	7.4 (5.6)	–1.925	0.054
Inattention	12.8 (7.8)	10.1 (6.3)	–1.838	0.066
Opposition/defiance	7.9 (5.0)	6.1 (4.4)	–2.179	0.029
Conduct disorder	1.6 (2.4)	1.5 (2.7)	–0.223	0.823
Total score	32.9 (16.2)	25.4 (15.9)	–2.260	0.024
CPRS	44.0 (21.3)	29.0 (15.4)	–3.304	0.001
Teacher				
T-*DSM-IV*-S				
Hyperactivity/impulsivity	11.4 (6.2)	8.4 (6.4)	–2.016	0.044
Inattention	14.1 (7.7)	11.4 (6.1)	–1.592	0.111
Opposition/defiance	8.1 (5.3)	5.6 (4.8)	–1.957	0.050
Conduct disorder	3.0 (3.1)	1.3 (1.9)	–1.894	0.058
Total score	36.9 (17.2)	26.9 (15.4)	–2.540	0.011
CTRS	35.2 (13.0)	28.0 (15.9)	–2.469	0.014
BGT	9.8 (4.2)	6.3 (3.4)	–3.270	0.001

*Wilcoxon signed rank test.

vs 29.0 [15.4], $P = 0.001$, respectively); the CTRS scores also decreased significantly (35.2 [13.0] vs 28.0 [15.9]; $P = 0.014$) (**Table II**).

The quantitative values of SPECT observed before treatment compared with those observed after 3 months of MPH treatment were not found to be statistically significantly different in any areas of the brain. After MPH treatment, existing brain perfusion disorders became normal in 9 patients (42.9%), perfusion did not change in 5 patients (23.8%), normal brain perfusion became

disrupted in 3 patients (14.3%), and new perfusion disorders were added to the existing disorders in 4 patients (19.0%) (**Table III**).

After 3 months of treatment with MPH, 12 patients (57.1%) showed no change in EEG activity, 5 (23.8%) showed improvement, and 4 (19.0%) showed worsening activity (**Table III**).

Patients who had improvement or no worsening on EEG after MPH treatment improved significantly in regard to mean (SD) CTRS scores after MPH treatment compared with before treatment (25.9 [14.3] vs 35.0 [14.4]; $P = 003$) and the total T-*DSM-IV*-S scores completed by the teachers (25.1 [14.2] vs 38.4 [18.7]; $P = 0.005$) (**Table IV**). No significant difference was found in these scores in the patients whose EEG findings showed deterioration after MPH treatment (**Table V**).

In the study, AEs were not monitored. However, there were no dropouts due to AEs.

DISCUSSION

Although psychostimulants are the first-line pharmacotherapy in patients with ADHD, their mechanism of action is not fully understood.[46] The purpose of this study was to examine the effect of MPH treatment on rCBF, electrical activity of the brain, and clinical symptoms. Based on a review of the literature, this is one of the few studies to investigate the treatment impact of MPH by combining SPECT and EEG techniques.

We examined the EEGs of children with ADHD before and after 3 months of treatment with MPH. After treatment, no changes in EEG activity were observed in 12 of the 21 children, improvement was observed in 5 children, and deterioration was observed in 4. Chabot et al[21] reported that of the 130 children with a diagnosis of ADHD enrolled in their study, 56.9% showed improvement in their EEG activity, 9.3% showed disruption, and 33.8% did not show any change after treatment with a stimulant. A significant decrease was found in BGT mistake scores after treatment compared with before treatment in all of the participants. Considering that deterioration in BGT scores typically is more significant in organic brain syndromes, recovery through treatment of electrical wave anomalies in the brain may have decreased the BGT mistake scores.

In the present study there was a significant decrease in the scores of the CPRS completed by the mothers and fathers ($P = 0.002$ and $P = 0.004$, respectively), the CTRS ($P = 0.003$), and the T-*DSM-IV*-S total scores completed by the mothers, fathers, and teachers ($P = 0.01$, $P = 0.03$, and $P = 0.005$, respectively) of the patients whose EEG disorders showed improvement after MPH treatment. The decreases in the scores may indicate improvement in the clinical symptoms of ADHD. Similarly, in other studies, significant improvement was found in the EEG activity of children with a diagnosis of ADHD who responded positively to stimulant treatment.[24,47] Gucuyener et al[48] compared 57 children with ADHD and active seizures with 62 children with ADHD and EEG abnormalities. The tolerability and efficacy of treatment with antiepileptic drugs combined with

Table III. Electroencephalography (EEG) and single-photon emission computed tomography (SPECT) findings before and after 3 months of treatment with methylphenidate in children with attention-deficit/hyperactivity disorder (N = 21).

	EEG		SPECT	
Patient	Before Treatment	After Treatment	Before Treatment	After Treatment
1	Severe paroxysmal abnormality	Severe paroxysmal abnormality	Right temporobasal lobe hypoperfusion	Decreased right posterior parietal lobe perfusion, normalization of right temporobasal lobe perfusion
2	Normal	Normal	Normal perfusion	Decreased right cerebellum, occipital cortex, temporal lobe, and frontobasal lobe perfusion
3	Severe paroxysmal abnormality	Mild paroxysmal abnormality	Right temporobasal and bilateral frontal lobe hypoperfusion	Normal perfusion
4	Normal	Normal	Right temporobasal lobe hypoperfusion	Decreased right cerebellum, frontobasal and temporobasal lobe perfusion
5	Normal	Normal	Nonhomogeneous perfusion	Nonhomogeneous perfusion
6	Normal	Mild paroxysmal abnormality	Right temporal and frontal basal lobe hypoperfusion	Normal perfusion
7	Normal	Normal	Right frontal basal, parietal, and occipital lobe hypoperfusion	Normal perfusion
8	Normal	Severe paroxysmal abnormality	Bilateral temporal and parietal lobe hypoperfusion	Normal perfusion
9	Normal	Normal	Right temporal and frontal basal lobe hypoperfusion	Normal perfusion
10	Normal	Normal	Normal perfusion	Normal perfusion
11	Normal	Normal	Right temporobasal and frontal basal lobe hypoperfusion	Normal perfusion
12	Normal	Mild paroxysmal abnormality	Normal perfusion	Normal perfusion

(continued)

Table III. (Continued)

Patient	EEG		SPECT	
	Before Treatment	After Treatment	Before Treatment	After Treatment
13	Severe paroxysmal abnormality	Normal	Bilateral temporal and parietal lobe hypoperfusion	Normal perfusion
14	Mild paroxysmal abnormality	Normal	Normal perfusion	Decreased right temporal and frontobasal lobe perfusion
15	Severe paroxysmal abnormality	Moderate paroxysmal abnormality	Normal perfusion	Normal perfusion
16	Mild paroxysmal abnormality	Severe paroxysmal abnormality	Bilateral frontal lobe and right temporal lobe hypoperfusion	Decreased left temporal lobe perfusion
17	Moderate paroxysmal abnormality	Normal	Left temporobasal lobe hypoperfusion	Decreased right frontobasal lobe perfusion
18	Normal	Normal	Bilateral temporal and posterior parietal lobe hypoperfusion	Normal perfusion
19	Normal	Normal	Left parietal and occipital lobe hypoperfusion	Left parietal and occipital lobe hypoperfusion
20	Normal	Normal	Normal perfusion	Decreased left temporal lobe perfusion
21	Normal	Normal	Right temporobasal lobe hypoperfusion	Normal perfusion

MPH were determined by assessing seizure frequency, changes in ADHD symptoms, CPRS and CTRS scores, EEG differences, and AEs. The mean CPRS, CTRS, and total ADHD symptom scores at the beginning and end of the study were significantly different ($P = 0.05$, $P = 0.05$, and $P = 0.001$, respectively). Seizure frequency did not change from baseline. The authors concluded that MPH was well-tolerated and effective in children with ADHD and concomitant active seizures or EEG abnormalities.

In the present study, compared with pretreatment, no statistically significant differences were found after MPH treatment in any of the quantitative values in the areas of the brain examined using SPECT. SPECT showed 9 patients who had decreased rCBF before treatment had normal rCBF after MPH treatment. Specifically, low rCBF in the right frontotemporal areas became normal after treatment with MPH. Psychostimulants are believed to be effective in the treatment of ADHD by increasing perfusion in the frontal regions of the brain and thereby increasing dopamine and noradrenaline con-

Table IV. Findings before and after 3 months of methylphenidate treatment on the Turgay *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*)-based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-*DSM-IV*-S), the Conners' Parent Rating Scale (CPRS), the Conners' Teacher Rating Scale (CTRS), and the Bender Visual-Motor Gestalt Test (BGT) in children who improved or showed no change in electroencephalography findings after treatment (n = 17). Data are mean (SD).

Psychometric Test	Before Treatment	After Treatment	Z*	*P*
Mother				
T-*DSM-IV*-S				
Hyperactivity/impulsivity	14.0 (7.4)	9.5 (6.9)	−2.16	0.03
Inattention	11.6 (6.8)	7.1 (5.3)	−2.26	0.02
Opposition/defiance	7.7 (4.7)	6.1 (5.2)	−1.77	0.07
Conduct disorder	3.4 (5.4)	2.4 (4.2)	−1.38	0.16
Total score	36.7 (18.8)	25.8 (18.9)	−2.55	0.01
CPRS	42.7 (17.2)	29.7 (16.6)	−3.10	0.002
Father				
T-*DSM-IV*-S				
Hyperactivity/impulsivity	13.4 (7.9)	11.1 (6.8)	−1.48	0.13
Inattention	10.8 (6.7)	6.9 (5.9)	−2.04	0.04
Opposition/defiance	8.3 (5.6)	6.4 (4.8)	−1.88	0.05
Conduct disorder	1.7 (2.7)	1.7 (3.0)	−0.07	0.91
Total score	34.1 (17.9)	26.2 (18.1)	−2.07	0.03
CPRS	41.9 (23.7)	29.4 (16.8)	−2.87	0.004
Teacher				
T-*DSM-IV*-S				
Hyperactivity/impulsivity	15.4 (8.2)	11.4 (6.1)	−2.24	0.02
Inattention	11.7 (6.7)	7.8 (5.7)	−2.07	0.03
Opposition/defiance	8.5 (6.0)	4.5 (4.5)	−2.61	0.009
Conduct disorder	2.8 (3.1)	1.2 (1.9)	−1.52	0.12
Total score	38.4 (18.7)	25.1 (14.2)	−2.78	0.005
CTRS	35.0 (14.4)	25.9 (14.3)	−2.92	0.003
BGT	9.7 (4.3)	5.8 (3.0)	−2.90	0.004

*Wilcoxon signed rank test.

centrations.[49] Lou et al[15] conducted a study of MPH in 2 groups of patients: 6 patients with ADHD alone and 13 patients with ADHD in combination with other neurologic symptoms. Inhalation of ^{133}Xenon and emission tomography were used in both treatment groups, as well as in a control group, to assess rCBF. Significant hypoperfusion was found in the right striatum in patients with ADHD and in both striatal regions in patients with ADHD

Table V. Findings before and after 3 months of methylphenidate treatment on the Turgay *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*)-based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-*DSM-IV*-S), the Conners' Parent Rating Scale (CPRS), the Conners' Teacher Rating Scale (CTRS), and the Bender Visual-Motor Gestalt Test (BGT) in children who showed deterioration in electroencephalography findings after 3 months of treatment (n = 4). Data are mean (SD).

Psychometric Test	Before Treatment	After Treatment	Z*	*P*
Mother				
T-*DSM-IV*-S				
Hyperactivity/impulsivity	11.4 (6.2)	12.8 (5.8)	–0.542	0.5
Inattention	14.6 (3.5)	10.0 (5.5)	–1.762	0.07
Opposition/defiance	8.8 (2.9)	6.6 (4.4)	–1.604	0.1
Conduct disorder	1.4 (1.9)	1.6 (1.8)	–0.184	0.8
Total score	36.2 (3.4)	31.0 (15.0)	–0.405	0.6
CPRS	41.0 (13.6)	33.4 (16.0)	–0.674	0.5
Father				
T-*DSM-IV*-S				
Hyperactivity/impulsivity	11.0 (8.0)	7.0 (3.1)	–1.214	0.2
Inattention	10.4 (4.2)	9.2 (4.6)	–0.135	0.8
Opposition/defiance	6.6 (2.6)	5.6 (3.2)	–1.342	0.1
Conduct disorder	1.2 (1.0)	1.0 (1.7)	–0.272	0.7
Total score	29.2 (9.1)	23.0 (5.5)	–0.677	0.4
CPRS	50.8 (9.8)	29.4 (10.8)	–1.753	0.08
Teacher				
T-*DSM-IV*-S				
Hyperactivity/impulsivity	10.2 (4.8)	11.6 (7.1)	–0.135	0.8
Inattention	10.8 (4.7)	10.4 (8.8)	–0.184	0.8
Opposition/defiance	7.0 (1.8)	9.0 (4.4)	–1.461	0.1
Conduct disorder	4.0 (3.3)	1.8 (1.7)	–1.069	0.2
Total score	32.0 (11.4)	32.8 (19.3)	–0.135	0.8
CTRS	36.0 (9.0)	35.0 (20.7)	–0.135	0.8
BGT	10.4 (4.5)	8.4 (4.1)	–1.289	0.1

*Wilcoxon signed rank test.

and other neuropsychologic and neurologic symptoms. MPH was associated with increased blood flow to the striatal and posterior periventricular regions. Moreover, a cardinal feature of ADHD is low striatal activity, which was partially reversible with MPH treatment.[15]

In the present study, the mean mistake score on the BGT before MPH treatment decreased significantly after treatment (9.8 [4.2] vs 6.3 [3.4]; $P = 0.001$).

This finding suggests that MPH has an effect that increases the attention level in children with ADHD. BGT measures perception of a visual stimulant, visual motor coordination, and integration. In a study comparing the BGT mistake scores, children with ADHD scored higher than those with Tourette's syndrome; this situation is special to children with ADHD.[50]

In our study, the second subsection duration of the Stroop test decreased significantly compared with pretreatment ($Z = -2.242$; $P < 0.05$). These findings demonstrate the positive effect of MPH treatment on executive functioning in ADHD. Our findings are similar to those of other studies.[5,51]

As discussed previously, the mean scores on the CPRS, CTRS, and T-*DSM-IV*-S all decreased significantly after treatment. Behavioral evaluation scales contribute to both diagnosis and follow-up of a variety of behaviors. The sensitivity and specificity of these scales should be proven. In this study, we used such scales to evaluate ADHD symptoms of children, both at home and at school, and with MPH treatment. The decrease in symptoms in some of the patients indicated apparent improvement in ADHD. Clinical and experimental studies with placebo controls have found stimulant treatment to be beneficial for ~80% of patients with ADHD.[3,4] The data obtained in our study found similarities with data from other studies that reported MPH treatment to be effective in improving ADHD symptoms.[3,46]

Limitations

This was a prospective cohort study in which the patients served as their own controls. This may have introduced bias into the study, as there could have been changes over time that would be misclassified as being related to MPH treatment. In addition, patients and investigators were not blind to the fact that the MPH was being used. This may have led to misclassification or recall bias.

Using SPECT, which is an invasive method, limited the number of the patients who agreed to take part in the study. Although 60 patients were selected based on the inclusion criteria, only 21 of the patients and their parents agreed to participate after reading the written informed consent form. Although the sample size was thought to be inadequate to perform a power calculation, information about 21 patients may be clinically useful. Basing the evaluation of compliance solely on the verbal forms of parents can be considered as a significant limitation of the study.

Throughout the 3-month treatment period, parents were asked about the occurrence of AEs that might be associated with MPH in the monthly clinical evaluations. No patient discontinued use of the drug due to AEs. Another significant limitation of our study was not evaluating the AEs of each patient with a standard AE evaluation checklist.

Increasing the number of patients and evaluating the effects of MPH treatment on attention and executive functioning using more neuropsychological test batteries will contribute to determining the effect of MPH in children with ADHD.

CONCLUSIONS

MPH use over 3 months was associated with improved visual-motor function and behavioral disorders in these children and adolescents with ADHD. However, no significant difference in rCBF or electrical activity in the brain was observed in this small study.

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